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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,988	07/05/2001	Yuta Nakai	210669US0	1677

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 08/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/897,988	Applicant(s) NAKAI ET AL.	
	Examiner Maria B. Marvich	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: 4 .

DETAILED ACTION

Specification

A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required (excluding claims). The substitute specification filed must be accompanied by a statement that it contains no new matter.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ciccognani et al.

Ciccognani et al. teach using a strain of E. coli (RG145) with elevated levels of cytochrome bo quinol oxidases (a SoxM oxidase) and that lacks the cytochrome bd quinol oxidases (page 1, line 1-3). The E.coli strain RG145 contains a chromosomal deletion that results in the inability of the cell to express cydA and a cosmid containing the cyo operon resulting in over expression of the cytochrome bd complex (page 2, section 3.1). This microorganism is used to produce of cytochrome b and cytochrome o as well as copper and methods for their production is presented (page 2 section 3.2 and 3.3).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "wherein the Sox M type oxidase" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a target substance utilizing E. coli with an enhanced SoxM type oxidase or NDH-I activity and deficient cytochrome bo type oxidase or NDHII activity, it does not provide an enabling disclosure for said method using any microorganism with any enzyme constituting the respiratory chain pathway with high energy that is enhanced and/or with low energy efficiency that is deficient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. The alteration of any enzyme of the respiratory pathway for the generation of a microorganism to be utilized in a method for the production of target substances is unpredictable. Recombinant technology as claimed in the present invention includes mutation in and deletion as well as the introduction of heterologous genes and regulatory genes in combination with natural genes. Metabolic engineering is an unpredictable art as discussed in Bailey et al. Complex cellular responses to genetic perturbations can complicate predictive design and thus few examples of successful systems based on metabolic engineering exist (page 1668, column 1). These complex cellular responses include an inability to anticipate further reactions which leads to iterative cycles of genetic modifications, an inability to predict metabolic consequences of transfer of heterologous genes into the cell, rearrangements and deletions of chromosomal and plasmid DNA.

2) State of the art. The state of the art at the time of invention included knowledge of respiration systems in E.coli rooted in many years of analysis. The analysis of energetic efficiency and the detailed analysis of respiratory pathways are still under study. The discernment of energetic efficiency is an unknown and contested topic. Therefore, determining what enzymes other than NDH-I, NDH-II, cytochrome bd and cytochrome bo to generate the starting strains is an unpredictable art. Neijssel et al. teaches that much heated debates exist about the assessment of respiration efficiency due to the complexity of the system. They teach that the efficiency of energy conservation using intact cells could not (and still cannot) be determined as simply as in mitochondria and cell-free preparations yielded unreasonably low

P/O ratios (page 180 line 3-7). Again the only exemplified systems are the NDH and bd/bo type oxidases. Thus determining any enzyme in the respiration chain that would provide the ability to perform the invention is unpredictable.

3) Number of working examples. The specification provides by way of example of claimed invention developing a system with amplified bo type oxides (cyo operon) or deletion of the gene encoding NDH-II. Several means of amplification are provided including gene amplification, promoter mutations. Homologous recombination and mutation of ndhII are suggested to create a deficiency in this enzyme. Overproducing cyo strains and deficient NDHII E. coli strains are exemplified. The effect of these strains in the production of L-lysine, l-phenylalanine and L-threonine is also provided as to strains, growth conditions, and assays for production.

4) Amount of guidance provided by applicants. Guidance has been provided for the generation of E. coli with specific alterations in the expression levels of bo and bd type oxidases as well as NDHI and NDHII strains. This includes guidance as to the means of over expression through gene amplification, promoter enhancement and mutagenesis of the bo type oxidase. Reduction or elimination of NDH-II is suggested through mutation or recombination. It is said that specific example of microorganisms include those in which SoxM or NDH-1 are enhanced and cytochrome bd or NDH-II are reduced. The guidance provided by the applicants does not provide for how to predict what other strains of bacteria with altered high and low efficiency enzymes would be suitable.

5) Nature of invention. The invention recites a method for producing target substances through genetic manipulation of bacterial strains. It relies primarily on the fields of microbiology.

6) Level of skill in the art. The level of skill in the art covering this invention was not high at the time of invention.

7) Scope of the invention. This invention is broad in scope in that it recites a method to produce any target substance through genetic manipulation of any enzyme in the respiratory pathway

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Maria B Marvich, PhD
Examiner
Art Unit 1636

August 7, 2002

DAVID GUZO
PRIMARY EXAMINER